Longitudinal development of hippocampal subfields during early to mid-childhood

Kelsey Canada, Fengji Geng, Gregory R. Hancock, & Tracy Riggins
University of Maryland, College Park

Neurocognitive Development Lab

Introduction

Early childhood is a time of rapid, significant change in episodic memory abilities, with prior research linking gains in memory to the hippocampus (HPC).

HPC is a heterogeneous subcortical structure within the medial temporal lobe consisting of the dentate gyrus (DG), cornu ammonis (CA) 1-4, and the subiculum (Sub). Work from animal models suggests that these subfields differ in their developmental trajectories early in life (Lavenex and Lavanex, 2013).

Cross-sectional research in young children has suggested differences in the volume of HPC subfields between 4- to 8-years (Canada et al., in press), with age-related differences varying along the longitudinal axis (i.e., within HPC head and body; Riggins et al., 2018).

Yet, currently lacking is a detailed understanding of the developmental trajectory of these heterogenous subfields during early childhood, which could contribute to understanding of memory development.

The current longitudinal study examined *developmental changes* in HPC subfields between 4- to 8-years of age by modeling subfield growth in both head and body of the HPC using multi-cohort latent growth models.

Methods

Participants

- A total of 165 4- to- 8-year-old children (88 females, 77 males) provided 270 useable ultra-high resolution structural MRI scans (39 had three scans, 27 had two scans, and 99 had one scan) for this accelerated longitudinal design (two cohorts at three time points).

- Cohort 1 was recruited at age 4, providing data at ages 4, 5, and 6 (M_{age} at T1= 4.40 yrs; M_{age} at T2= 5.46 yrs, M_{age} at T3 = 6.44 yrs). Cohort 2 was recruited at age 6, providing data at ages 6, 7, and 8 (M_{age} at T1= 6.36 yrs; M_{age} at T2= 7.32 yrs, M_{age} at T3 = 8.47 yrs).

MRI Data Acquisition and Analyses

MRI Data Collection

- Ultra-high resolution (.4mm x .4mm x 2mm) structural scans of medial temporal lobe (MTL) were acquired with a T2-weighted fast spin echo sequence (TR=4120ms, TE=41ms, 24 slices, 149 degree flip angle).

MRI Data Processing and Analysis

- Bilateral Sub, CA1, and CA2-4/DG volumes in HPC head and body were derived using a protocol adapted from Joie et al. (2010) and used in conjunction with the Automatic Segmentation of Hippocampal Subfields software (ASHS, Yushkevich et al., 2014) to yield volumes for all participants. All resulting segmentations were checked manually. Twelve subfield volumes per participant per timepoint were extracted from acceptable segmentations.

Statistical Analyses

Structural Equation Modeling (SEM)

- Multi-group latent growth modeling (LGM; Ghisletta and McArdle, 2001) was used in MPlus (v8; Muthén and Muthén).

- Latent factors of each subfield in HPC head and body were identified by left and right hemisphere measures (e.g., indicator variables for CA2-4/DG in HPC head were left and right CA2-4/DG in HPC head) for each age (i.e., CA2-4/DG in HPC head at age 4, 5, 6, 7, and 8), with each cohort modeled separately.

- Spline models were fit to allow for the mean change in subfield volume between each age-point to be estimated. Spline models break an observed curvature pattern of change (i.e., non-linear growth) into piecewise linear components and are useful for comparing rates of change at different periods in time.

- Means and variances for the intercept, a slope between time 1 and time 2, and a slope between time 2 and time 3 were estimated to examine the developmental trajectory of each subfield.

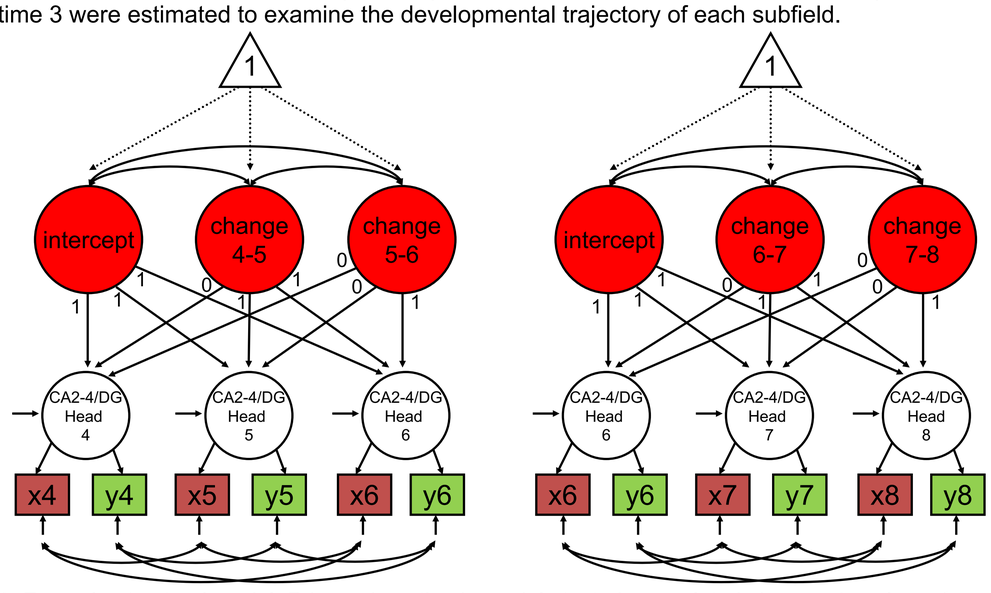

Figure 1. Example structural model. Primary hypothesis models tested age-related changes in volume for each HPC subfield separately in head and body for each cohort. x= region of interest (ROI) in right hemisphere, y= ROI in left hemisphere.

Results

Model Fit

χ2(8) = 4.63 – 16.93, *p*s > .05 except CA1 in HPC body for 6yo cohort (p = 0.03)
CFI = All models > .94
RMSEA = 0.00 - 0.10. CA1 in HPC head for 4yo cohort = 0.08, CA2-4/DG in HPC body for 4yo cohort = 0.09, CA1 in HPC body for 6yo cohort = 0.10
Note: Fit criteria demonstrate good model fit. χ2, fit criteria: p > .05; CFI—comparative fit index, fit criteria: ≥ 0.90; RMSEA—root mean square error of approximation, fit criteria: ≤ 0.05.

HPC Head

CA2-4/DG:
- Initial volumes differed for 4 & 6 year olds
- Volume increased from 4 to 5 years
- Volume increased from 6 to 7 years
- No change overall from 7 to 8 years, but trajectories differed between children

CA1 & Sub:
- Initial volumes differed for 4 year olds, but not 6 year olds
- No changes in volume or differences in children's trajectories from 4 to 8 years

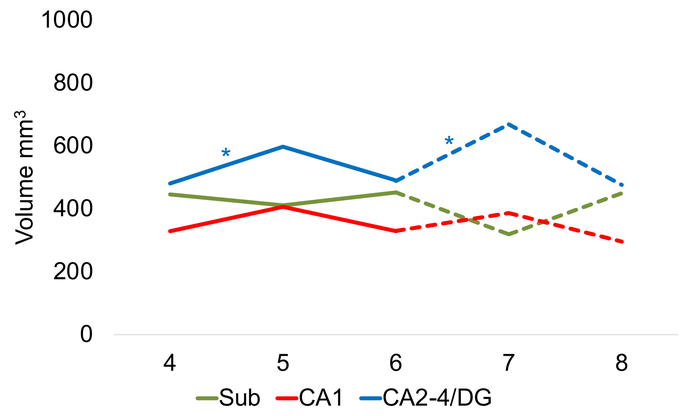

Figure 2. Estimated developmental trajectories of growth in HPC head for Sub (green), CA1 (red), and CA2-4/DG (blue). Solid lines represent 4yo cohort, dashed lines represent 6yo cohort.*p < 0.05.

HPC Body

CA2-4/DG:
- Initial volumes differed for 4 & 6 year olds
- Volume increased from 5 to 6 years

CA1:
- Initial volumes differed for 4 year olds, but not 6 year olds
- Volume increased from 5 to 6 years

Sub:
- Initial volumes differed for 4 year olds, but not 6 year olds
- Individual trajectories from 4 to 5 years varied significantly between individuals

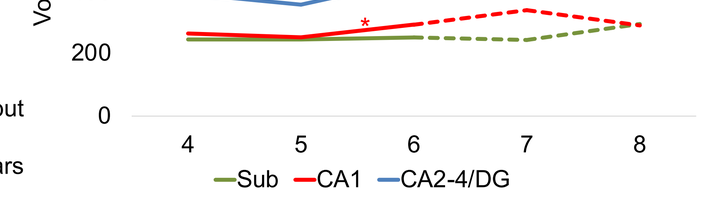

Figure 3. Estimated developmental trajectories of growth in HPC body for Sub (green), CA1 (red), and CA2-4/DG (blue). Solid lines represent 4yo cohort, dashed lines represent 6yo cohort.*p < 0.05.

Discussion

The current report offers exciting findings regarding the structural development of HPC subfields along the longitudinal axis during early to mid-childhood.

Results indicate a great deal of heterogeneity in developmental trajectories. Sub shows no changes across this developmental period, CA1 shows increases in volume from 5-6 in HPC body, and CA2-4/DG shows the most prolonged development, with increases observed from 5-6 in HPC head, and increases in volume from 4 to 5 and 6 to 7 in HPC body.

Our findings are consistent with work in non-human primates suggesting the relatively early structural maturation of Sub, more prolonged development of CA1, and the most prolonged development in CA3/DG (Lavenex and Lavenex, 2013).

While this report offers insight into the structural development of HPC subfields during early to mid-childhood, future work should seek to make connections to findings of continued change in both subfields and memory into adolescence (e.g., Lee et al., 2014) and adulthood (Daugherty et al., 2017) in order to gain a comprehensive understanding of the development of the neural mechanisms supporting memory.

References

1. Canada, Ngo, Newcombe, Geng, & Riggins. (in press). *Cerebral Cortex.*
2. Joie, Fouquet, Mézenge, Landeau, Villain, Mevel, Pélerin, Eustache, Desgranges, & Chételat. (2010). *NeuroImage*, *53*(2), 506–14.
3. Lavenex & Lavenex. (2013). *Behav Brain Res*, *254*:8–21.
4. Ghisletta &McArdle JJ. (2001). *Struct Equ Model. 8*:531–55.
5. Muthén and Muthén. (1998-2012). Mplus User's Guide. Eighth Edition. Los Angeles, CA: Muthén & Muthén.
6. Riggins, Geng, Botdorf, Canada, Cox, & Hancock (2018). *Neuroimage. 174:*127–137.
7. Yushkevich, Pluta, Wang, Ding, Xie, Gertje, Mancuso, Kliot, Das, & Wolk, D.A. (2014). *Hum Brain Mapp*, *36*(1), 258–87.
8. Lee, Ekstrom, & Ghetti. (2014). *Neuroimage. 94:*162–171.
9. Daugherty, Flinn, & Ofen. (2017). *Neuroimage. 153:*75–85.

Acknowledgements

Thank you to the families that participated in this research study and to members of the Neurocognitive Development Lab for assistance with data collection. Support for this research was provided by NICHD under Grant HD079518 (TR).

For questions or comments, please contact kcanada@umd.edu.